

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C08F 220/28, 220/38, A61L 33/00, C08F 246/00</b>	<b>A1</b>	(11) International Publication Number: <b>WO 97/41164</b>
		(43) International Publication Date: 6 November 1997 (06.11.97)

(21) International Application Number: PCT/GB97/01173

(22) International Filing Date: 30 April 1997 (30.04.97)

(30) Priority Data:  
9608882.8 30 April 1996 (30.04.96) GB

(71)(72) Applicants and Inventors: LUTHRA, Ajay, Kumar [GB/GB]; 219 Somervell Road, South Harrow, Middlesex HA2 8UA (GB). SANDHU, Shivpal, Singh [GB/GB]; 63 Lascelles Road, Slough, Berkshire SL3 7PW (GB).

(74) Agent: URQUHART-DYKES &amp; LORD (READING); 1 Richfield Place, 12 Richfield Avenue, Reading RG1 8EQ (GB).

(81) Designated States: AU, CA, GB, JP, NO, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published***With international search report.  
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: NON-THROMBOGENIC AND ANTI-THROMBOGENIC POLYMERS

## (57) Abstract

Polymers having non-thrombogenic properties can be prepared by copolymerising monomers of at least three classes selected from (a) monomers having sulphate groups, (b) monomers having sulphonate groups, (c) monomers having sulphamate groups, and (d) monomers having polyoxyalkylene ether groups, (e) monomers having zwitterionic groups. The monomers can additionally be provided with anti-thrombogenic properties by including an additional comonomer having a pendant heparin (or hirudin, warfarin or hyaluronic acid) group. The polymers can be used as coating materials for medical devices, such as tubing or connectors, in order to provide them with non-thrombogenic, and optionally anti-thrombogenic, properties.

**FOR THE PURPOSES OF INFORMATION ONLY**

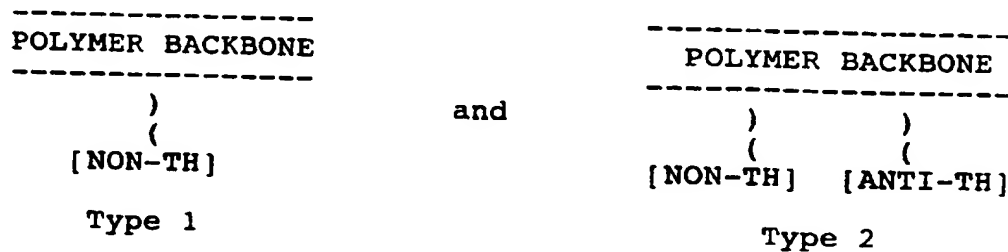
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# NON-THROMBOGENIC AND ANTI-THROMBOGENIC POLYMERS

## SUMMARY OF INVENTION

This invention relates to the synthesis of polymers which contain non-thrombogenic (NON-TH) as well as anti-thrombogenic (ANTI-TH) properties. Such polymers can be conveniently represented as follows:



In schematic diagrams of this kind, as used herein, the designated side chains or groups can occur in any order and in any relative proportions along the polymer backbone.

In polymers of Type 1 the non-thrombogenic (NON-TH) component may consist of non-ionic hydrophilic domains, ionic domains, zwitterionic domains or combinations of such domains. In novel Type 1 polymers in accordance with the invention, such non-thrombogenic components may be selected from, but are not limited to, polymerisable sulphonates, polymerisable sulphates, polymerisable N-sulphates (also known as sulphamates), polymerisable zwitterionic compounds, and polymerisable polyethylene glycols. When we synthesised polymers of Type 1, without the anti-thrombogenic component, and coated various medical devices, we found blood cell and protein deposition reduced by greater than 90%. Greatly reduced (>95%) activation

-2-

of white cells, platelets and complement was observed. This type of synthetic polymer can be described as a non-thrombogenic polymer.

The non-thrombogenic Type 1 polymer, as described, was synthesised with polymerisable Heparin to give a Type 2 polymer. Surprisingly, the activity of the heparin was retained in the Type 2 polymer and such polymers, when coated on to medical devices, had the additional property of reducing the thrombin-antithrombin complex concentration. This inclusion of heparin into the non-thrombogenic polymer gave a new polymer which additionally exhibited anti-thrombogenic properties.

Another aspect of this invention is the process by which the non-thrombogenic and anti-thrombogenic polymers are coated onto medical devices.

#### BACKGROUND TO THE INVENTION

There is a growing interest in the use of artificial materials in clinical practice where these materials are in continuous contact with blood. Medical devices made from these materials are required to perform in the harsh biological environment in a specific application, for a specific duration without stimulating a biological response which may prove to be detrimental. Hence, such devices are required to be accepted by the biological environment for a specific application and duration, ie need to be bioacceptable. Improvements in bioacceptability are highly desirable for medical devices manufactured from artificial materials. Such materials commonly include polyvinyl chloride, polyethylene, polypropylene, polyurethanes, polycarbonates, stainless steel, silicones and the like. The biological response to blood contact with an artificial surface can be regarded in terms of

different contributions from protein, platelet and blood cell deposition, together with platelet and blood activation leading to thrombus formation.

Many investigations have been carried out to prevent an artificial surface from provoking thrombus formation, ie to form a bioacceptable surface. Such investigations include the use of polymers which are natural, hydrophilic, hydrophobic, zwitterionic and charged (anionic and cationic). These types of polymers are non-thrombogenic, have had limited success and therefore application. Surface modification of an artificial material by heparin (ie formation of an anti-thrombogenic surface) has also proved to be intractable. Although clot formation has been reduced, platelet activation and blood cell activation are however still prevalent. Similarly, a particular artificial surface may be resistant to protein, platelet and blood cell deposition but may still activate blood constituents.

Each surface, whether non-thrombogenic or anti-thrombogenic, has its own profile of desirable bioacceptable properties, but no particular material possesses the full spectrum of the desired properties.

Additional disadvantages of some of the known approaches are (i) the procedures used to produce these materials are complex, (ii) the methods of applying these materials to the medical device are elaborate, and (iii) these processes utilise reagents which are highly toxic, even in minute quantities.

In a new approach to the problem of finding suitable bioacceptable materials, we have synthesised a novel non-thrombogenic polymer, and have also modified non-thrombogenic polymers by incorporating a polymerisable anti-thrombogenic compound, exemplified by polymerisable heparin. It was found that heparin activity was maintained,

while the non-thrombogenicity of the polymer component was prevalent. Other known biologically active anti-thrombogenic compounds include hirudin, warfarin and hyaluronic acid, and can be used in the same manner as the polymerisable heparin.

#### THE INVENTION

One embodiment of the present invention provides polymers comprising a polymer backbone having pendant groups, obtainable by polymerising monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

- (a) monomers having sulphate groups
- (b) monomers having sulphonate groups
- (c) monomers having sulphamate groups, and
- (d) monomers having polyoxyalkylene ether groups.

Another embodiment of the present invention provides polymers comprising a polymer backbone having pendant groups, obtainable by polymerising monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

- (a) monomers having sulphate groups
- (b) monomers having sulphonate groups
- (c) monomers having sulphamate groups
- (d) monomers having polyoxyalkylene ether groups, and
- (e) monomers having zwitterionic groups.

A further embodiment of the present invention provides a method of forming a coating of a polymer as described above on a medical device by forming an ungelled partial polymer by reacting a solution of an amine polymer with a crosslinking agent, activating the medical device by solution coating with said partial polymer, and depositing the polymer on the resulting activated medical device.

The present invention also provides a coating material comprising a polymer as described above.

Without wishing to be bound by any theory or explanation of the invention, it appears that non-thrombogenic surfaces have an important impact on the first event of contact of blood with an artificial surface. This event occurs almost instantaneously and consists of protein adsorption. Subsequent events are largely determined by interactions of blood with the adsorbed protein. The nature of the artificial surface determines the manner and extent of protein attachment.

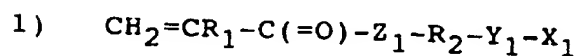
For hydrophobic surfaces, attachment occurs by hydrophobic interactions with the protein, which causes conformational change of the adsorbed protein, exposing sites for protein interaction resulting in further protein adsorption. The next sequence of events has a pronounced influence in promoting platelet adsorption/activation and white cell adsorption/activation. The consequence of these events is the formation of thrombus.

Protein adsorption on hydrophilic surfaces is more readily and rapidly reversible than on hydrophobic surfaces. The extent of reversibility is determined by the nature of the chemical bond in the equilibrium state. At high states of reversibility, protein adsorption is not prevalent and consequently platelet and white cell adsorption/activation is prevented. Therefore, thrombus formation is averted.

This type of hydrophilic surface is regarded as being non-thrombogenic and in this respect we have found a new artificial hydrophilic polymer with at least three different types of hydrophilic groups which include, but are not restricted to, sulphonate, sulphate, N-sulphate (sulphamate) or zwitterionic groups, and polyethylene glycol or glycol ether units in the same polymer backbone.

In one embodiment of the present invention the non-thrombogenic polymer is obtainable by radical polymerisation, preferably of monomers having reactive carbon-carbon double bonds to form the polymer backbone and said monomer constituents containing, but not limited to, sulphonates, sulphates, N-sulphates (sulphamates), zwitterions, and polyethylene glycol units, these monomer constituents being contained in the same polymer composition. Such monomers may be separated into three groups.

The first group is based on monomers derived from acrylates or methacrylates of sulphonates, sulphates and N-sulphates:



Where  $\text{R}_1$  is H or  $\text{CH}_3$ ;  
 $\text{R}_2$  is a linear or branched alkylene of 2-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure  $[\text{CH}_2-\text{CHR}_1-\text{O}]_n$  where  $\text{R}_1$  is H or  $\text{CH}_3$  and  $n$  is from 2 to 50;  
 $\text{Z}_1$  is oxygen ( $-\text{O}-$ ) to give an ester linkage or secondary amine ( $-\text{NH}-$ ) to give an amide linkage;  
 $\text{Y}_1$  is ( $-\text{O}-$ ) or ( $-\text{NH}-$ ) or is absent; and  
 $\text{X}_1$  is sulphonate ( $-\text{SO}_3^-$ ) together with an acceptable balancing cation.

The second group is based on monomers derived from vinyl, allyl or methyl allyl, of sulphonates, sulphates and N-sulphates:



Where  $\text{R}_1$  is H or  $\text{CH}_3$ ;  
 $\text{R}_2$  is a linear or branched alkylene of 1-10 carbon atoms, phenylene, phenyl alkylene with



-7-

1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure  $[\text{CH}_2\text{-CHR}_1\text{-O}]_n$  where

$R_1$  is H or  $\text{CH}_3$  and  $n$  is from 2 to 50;

$Y_1$  is  $(\text{-O-})$  or  $(\text{-NH-})$  or is absent; and

$X_1$  is sulphonate  $(\text{-SO}_3^-)$

together with an acceptable balancing cation.

In both groups of monomers (1) and (2),

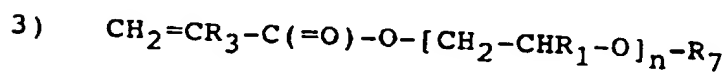
when  $Y_1$  is  $(\text{-O-})$ , the monomer terminates in a sulphate group;

$Y_1$  is  $(\text{-NH-})$ , the monomer terminates in a N-sulphate group;

$R_2$  and  $Y_1$  are not present, the monomer terminates in a sulphonate group;

$R_2$  is polyoxyalkylene and  $Y_1$  is not present, the monomer terminates in a sulphate group.

The third group of monomers is derived from acrylates or methacrylates of polyoxyalkylene glycols or glycol ethers:



Where  $R_3$  and  $R_4$ , which may be the same or different, are each H or  $\text{CH}_3$ ,  $R_7$  is H or alkyl with 1 to 5 carbon atoms, eg methyl, and  $n$  is an integer from 2 to 50.

Monomer examples incorporating sulphonate groups include, but are not restricted to, salts of:

2-sulphoethyl methacrylate, 2-sulphoethyl acrylate,  
3-sulphopropyl methacrylate, 3-sulphopropyl acrylate, vinyl  
sulphonate, allyl sulphonate, methyl allyl sulphonate,  
*p*-styrene sulphonate, 2-acrylamido-methylpropanesulphonate,

3-sulphopropyl ethoxy methacrylate, 3-sulphopropyl ethoxy acrylate, 3-sulphopropyl polyoxyalkylene methacrylate, 3-sulphopropyl polyoxyalkylene acrylate.

Similarly, examples of monomers terminating in sulphate groups include, and are not confined to, salts of:

2-sulphatoethyl methacrylate, 2-sulphatoethyl acrylate, 3-sulphatopropyl methacrylate, 3-sulphatopropyl acrylate, 4-sulphatobutyl methacrylate, 4-sulphatobutyl acrylate, allyl sulphate, methyl allyl sulphate, 3-buten-1-sulphate, 3-buten-2-sulphate, 2-methyl-2-propane-1-sulphate, 2-methyl-3-buten-1-sulphate, 3-methyl-3-buten-1-sulphate,, 2-sulphatoethyl methacrylamide, 2-sulphatoethyl acrylamide, 3-sulphatopropyl methacrylamide, 3-sulphatopropyl acrylamide, 4-sulphatobutyl methacrylamide, 4-sulphatobutyl acrylamide, sulphato polyoxyalkylene methacrylate, sulphato polyoxyalkylene acrylate.

Examples of N-sulphate (sulphamate) containing monomers include, but are not limited to, salts of:

2-sulphamatoethyl methacrylate, 2-sulphamatoethyl acrylate, 3-sulphamatopropyl methacrylate, 3-sulphamatopropyl acrylate, 4-sulphamatobutyl methacrylate, 4-sulphamatobutyl acrylate, allyl sulphamate, methyl allyl sulphamate, 2-sulphamatoethyl methacrylamide, 2-sulphamatoethyl acrylamide, 3-sulphamatopropyl methacrylamide, 3-sulphamatopropyl acrylamide, 4-sulphamatobutyl methacrylamide, 4-sulphamatobutyl acrylamide, sulphamato polyoxyalkylene methacrylate, sulphamato polyoxyalkylene acrylate.

The salts used to form the polymers according to the invention, including those listed above, will have an acceptable, especially physiologically acceptable, balancing cation such as an alkali metal (eg sodium) cation, or an ammonium or substituted ammonium cation. Hydrogen cations usually provide a polymer that is too acidic for the preferred use.

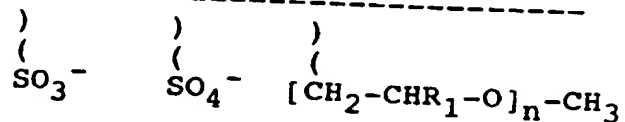
Other examples of non-thrombogenic polymers include those in which zwitterionic monomers may be included in the above formulations. For example, the non-thrombogenic polymers can contain any zwitterionic monomer as an integral part of the polymer backbone. The zwitterionic monomers may also be included in the non-thrombogenic/antithrombogenic polymers. Such zwitterionic monomers include, but are not limited to, 2-(methacryloyloxyethyl)-2'-(trimethylammonium) ethyl phosphate inner salt and dimethyl (2-methacryloylethyl)-[1-(2-sulphopropyl)] ammonium betaine inner salt.

A wide range of monomer compositions can be utilised in the formation of the non-thrombogenic polymer. Such a polymer may contain, and is not limited to, 3 to 4 different monomer constituents. The ter-polymer (3 different monomers) and the tetra-polymer (4 different monomers) are formulated from 3 or 4 respectively of at least one sulphate monomer type, at least one sulphonate monomer type, at least one sulphamate monomer type, and at least one polyoxyalkylene monomer type in the final polymer composition. This polymer composition can accordingly be schematically represented as follows, where the relative frequency and the order of occurrence of each monomer type are variable (being random co-polymers). In each instance anions shown are balanced by acceptable cations, such as those mentioned above.

a) ter-polymer

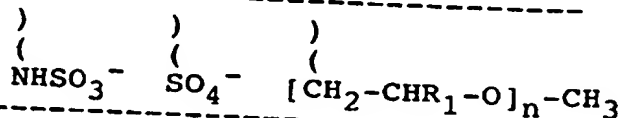
i)

POLYMER BACKBONE

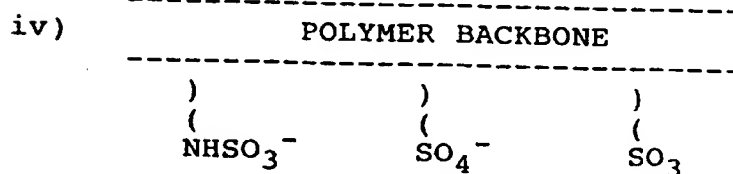
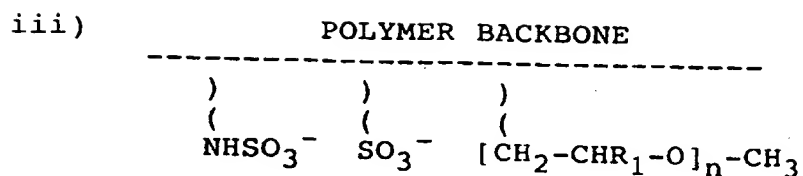


ii)

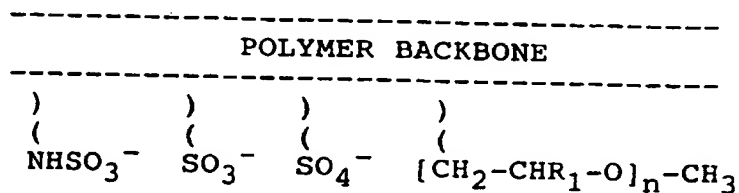
POLYMER BACKBONE



-10-



b) tetra-polymer



The above co-polymerised monomer compositions are examples of non-thrombogenic (NON-TH) polymers represented above as Type 1.

In another aspect of this invention the non-thrombogenic component is accompanied by a polymerisable anti-thrombogenic component such as polymerisable heparin in the same polymer backbone, and said anti-thrombogenic component in its bioactive form being carried by an integral part of the aforementioned polymer backbone.

Functionalisation of heparin by methacrylation of heparin is known (ACS Symposium Series 77; Carbohydrate Sulphates, 1978). Subsequent known polymerisations with other monomers give rise to anti-thrombogenic polymers only, containing no non-thrombogenic component (of the kind referred to herein).

This aspect of this invention accordingly provides a polymer containing non-thrombogenic and anti-thrombogenic constituents on the same polymer backbone. Preferred non-thrombogenic constituents may comprise sulphate, sulphamate, sulphonate,

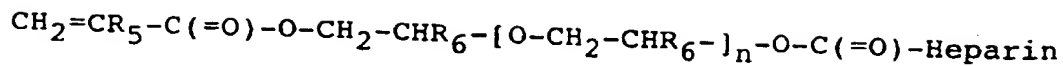
zwitterionic and polyoxyalkylene glycol and glycol ether, together with anti-thrombogenic constituents consisting of polymerisable heparin bearing carbon-carbon double bonds. Essentially the carbon-carbon double bond carried by the heparin moiety is polymerisable by a free radical process and may be by way of example vinyl, allyl, methyl allyl, acrylate or methacrylate. Heparin linked to a component containing a polymerisable carbon-carbon double bond is hereafter referred to as heparin monomer. Corresponding monomers in which the heparin is replaced by hirudin, warfarin or hyaluronic acid moieties may be used in like manner.

The favoured heparin monomers are those in which heparin is linked to a polyoxyalkylene methacrylate or polyoxyalkylene acrylate through an ester or carbonate linkage. The ester or carbonate linkage is formed by activating the hydroxyl terminating polyoxyalkylene methacrylate or acrylate with carbonyldiimidazole, forming the activated imidazolyl carbonate, which subsequently is either coupled to carboxylic groups of the heparin molecule to yield an ester linkage or coupled to hydroxyl groups of the heparin molecule to yield a carbonate linkage. This means of attaching the polyoxyalkylene methacrylate or acrylate group to heparin allows polymerisation of the heparin with the desired biological properties. Other coupling techniques as described in WO 91/16932 using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide result in linkages occurring on sulphate groups of the heparin, called a sulphonamide linkage. This coupling procedure results in poor biological properties since these N-sulphate and sulphate groups are important for binding to antithrombin.

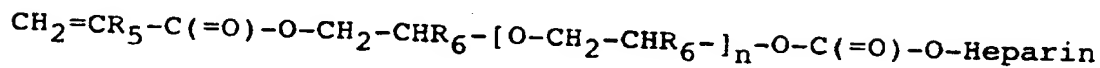
Preferred heparin monomers include those of the following formula:

-12-

(1) With ester linkage to heparin



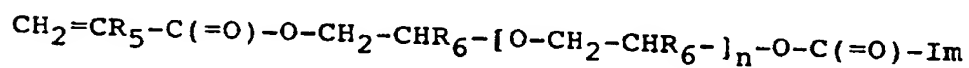
(2) With carbonate linkage to heparin



In both general formulae,  $\text{R}_5$  and  $\text{R}_6$ , which may be the same or different, are each H or  $\text{CH}_3$ ; and  $n$  is an integer from 0 to 49.

Particularly preferred heparin monomers are those derived from polyethylene oxide units, that is to say where  $\text{R}_2$  is H.

The heparin monomers (1) and (2), as above, are novel and are other aspects of this invention and may be produced by reacting hydroxyl terminated polyoxyalkylene with carbonyldiimidazole [ $\text{Im}-\text{C}(=\text{O})-\text{Im}$ ] to form the activated imidazolyl carbonate:



where  $\text{R}_5$ ,  $\text{R}_6$  and  $n$  have the meanings given above,

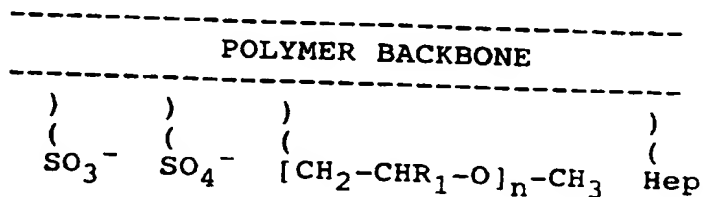
this being followed by the coupling of the activated imidazolyl carbonate to heparin under basic pH conditions using bicarbonate buffer at room temperature.

The heparin monomer is polymerised with the aforementioned monomer of sulphate, sulphamate, sulphonate and polyoxyalkylene, producing a polymer with both non-thrombogenic and anti-thrombogenic properties. This polymer composition may contain 4 to 5 of the different types of monomer constituent. The tetra-polymer (4 different monomer types) and the penta-polymer (5 different monomer types) are so formulated from 3 or 4 respectively of at least one sulphate monomer type, at least one sulphonate monomer type, at least one sulphamate

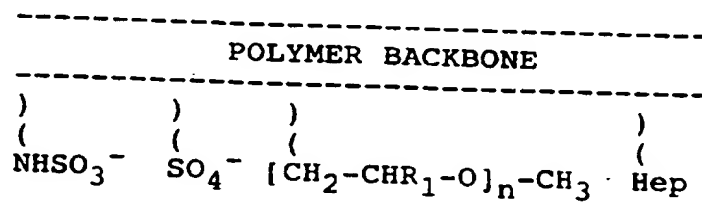
monomer type, and at least one polyoxyalkylene monomer type, together with at least one heparin monomer type, in the final polymer composition. This polymer composition can accordingly be schematically represented as follows, the relative frequency and the order of occurrence of each monomer type being variable. In each instance the anions shown are balanced by acceptable cations, such as those mentioned above.

a) tetra-polymer

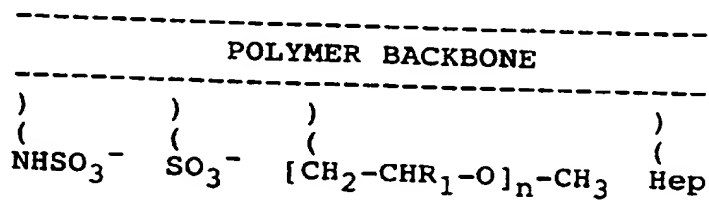
i)



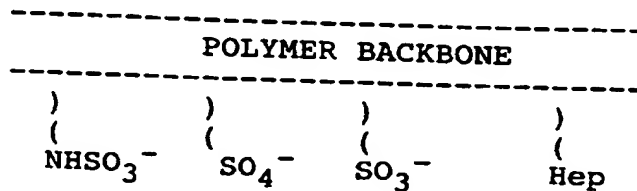
ii)



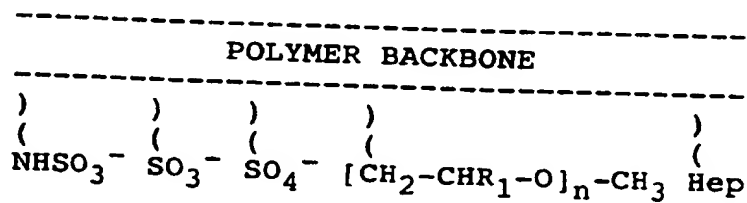
iii)



iv)



b) penta-polymer



These non-thrombogenic/anti-thrombogenic (NON-TH/ANTI-TH) polymers are of the kind represented above as Type 2.

Polymerisation may be carried out by conventional aqueous solution polymerisation using a water soluble initiator, such as potassium persulphate, after degassing the solution and under an inert gas, such as nitrogen. Reaction temperature for polymerisation is at room or elevated temperature, provided that the heparin biological activity is not affected. The preferred polymerisation temperature is one between 15 to 90°C, and generally a polymerisation temperature of 75°C is suitable. The polymer may be purified by conventional means, such as precipitation, filtration wash and dialysis.

The aforementioned non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer according to the invention is capable of being applied as a coating on medical devices for use in blood-contacting applications. In this regard, another aspect of this invention is the modification of polyethylene imine or other primary or secondary amino containing polymers to an extent that they form a stable attachment between the medical device and the non-thrombogenic polymer or the non-thrombogenic/ anti-thrombogenic polymer.

The use of unmodified polyethylene imine as an anchoring point for heparin is known, EP 0124676. In these processes the medical device requires chemical pre-treatment to allow attachment of polyethylene imine to occur. Additionally, multi-layers are built up on the device to ensure good coverage and to enhance the stability of the attachment. These are disadvantages which have severe impact on the performance and the coating process. The heparin attached is grafted onto the external polyethylene imine layer where surface covering is limited. There is predominately preferential ionic bonding of the heparin to the polyethylene imine. In such instances the heparin may be released from the surface. This coating



-15-

requires repeated steps to ensure that the polyethylene imine is bound effectively. This has the constraint of increasing the complexity of the process which results in high costs being incurred.

To overcome the disadvantages mentioned above we have devised a method for modifying primary or secondary amine polymers including polyethylene imine which can be attached to the medical device without any pre-treatment and can be carried out in a single step. This is achieved by increasing the molecular weight of the amine polymer, but to a limited extent, whereby the polymer does not gel, but remains in solution. This can, for instance, be achieved by crosslinking the amine, eg by treatment with a crosslinking agent, such as an alkylene diisocyanate, and/or with an alkyl isocyanate. The isocyanate crosslinking agents mentioned above react very quickly with the amino groups, but other crosslinking agents that are reactive with amino groups may be employed. These include, but are not limited to, diacids, diacid chlorides and cyclic anhydrides or dianhydrides. Generally there will be 4 to 16 carbon atoms between the active groups of the crosslinking agents. By increasing the hydrophobic nature of the amine polymer in this manner, it is capable of attaching to a suitable medical device sufficiently to allow attachment of the non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer. Hence the polymer coating process is essentially achieved in two steps, as opposed to multiple steps.

Attachment of the polymer to the polyethylene imine pre-coating can be enhanced by the incorporation of acrolein in the monomer feed for the non-thrombogenic/anti-thrombogenic polymer, giving aldehydic groups on the polymer backbone. These products are also novel. The aldehydic groups are allowed to react with amino groups on the modified polyethylene imine to form a Schiff's base which is reduced to form a stable covalent bond.

Alternatively the non-thrombogenic/anti-thrombogenic polymer may be attached to the modified polyethylene imine by ionic interaction.

The invention is illustrated by the following Examples, which are not intended to restrict the scope of the invention. In the Examples, concentrations are expressed as percentages weight/volume, i.e. grams weight per 100ml of solution.

The structure of the polymers whose preparation is identified in the following Examples can be confirmed by the presence of certain peaks in their FTIR spectra. These peaks include:

carbonate	1745.7 $\text{cm}^{-1}$
methacrylate	870 $\text{cm}^{-1}$ and 970 $\text{cm}^{-1}$
carboxylic acid (sodium salt or ester)	1609.8 $\text{cm}^{-1}$
carbohydrate hydroxyl	3500 $\text{cm}^{-1}$
C-O-C link in ester	1250 $\text{cm}^{-1}$

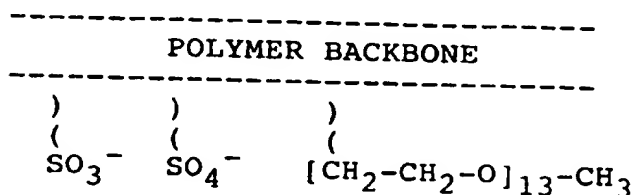
#### EXAMPLES 1 TO 5: THE FORMATION OF NON-THROMBOGENIC POLYMERS

##### Example 1

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 45g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 13g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the

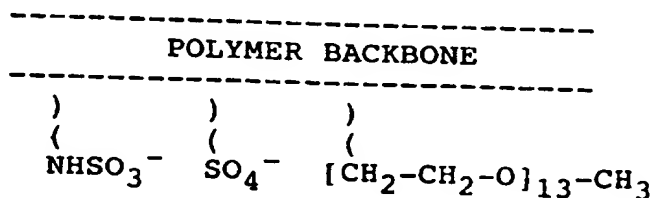
-17-

contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



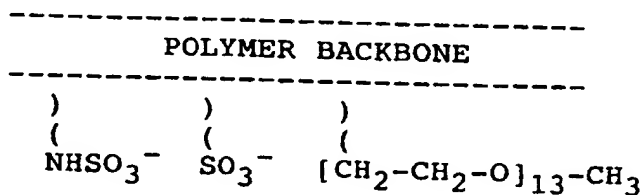
### Example 2

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 7.7g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 40.8g) and 2-sulphamatoethyl methacrylamide (25% aqueous solution, 22.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 3

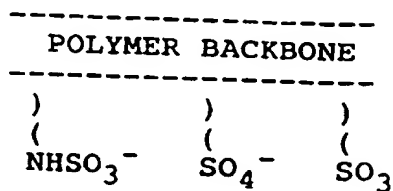
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 8.6g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 45.2g) and vinyl sulphononic acid sodium salt (25% aqueous solution, 14.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

Example 4

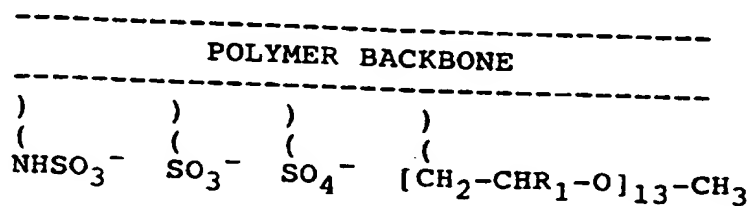
2-Sulphamatoethyl methacrylamide (25% aqueous solution, 16.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 59.6g) and vinyl sulphononic acid sodium salt (25% aqueous solution, 18.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of

-19-

the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

Example 5

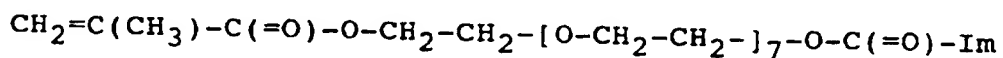
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13. 9.3g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 17.6g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 26.4g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 12.8g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



-20-

EXAMPLE 6: THE FORMATION OF ACTIVATED IMIDAZOYL CARBONATE

Hydroxy polyethyleneglycol methacrylate (PEG, n=7, 1.0g) was added drop-wise to carbonyldiimidazole (Im-C(=O)-Im; 0.5g) in anhydrous dichloromethane to form the activated imidazolyl carbonate:



The solution was stirred for 3 hours for the reaction to be completed and dichloromethane was removed on a rotary evaporator.

EXAMPLE 7: FORMATION OF HEPARIN MONOMER

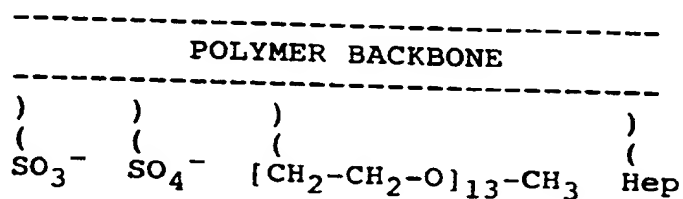
Heparin (injectable grade, 5.0g) was dissolved in 30ml of water. The heparin solution was then added to the activated imidazolyl carbonate formed in Example 6. The pH of the solution was adjusted to 8.5 to 9.0 by using potassium bicarbonate and the solution was stirred for 24 hours to form the heparin monomer. The solution was then adjusted to pH7 with HCl.

EXAMPLES 8 TO 12: THE FORMATION OF NON-THROMBOGENIC/ANTI-THROMBOGENIC POLYMERSExample 8

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 45g), vinyl sulphonic acid (25% aqueous solution, 13g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were

-21-

degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

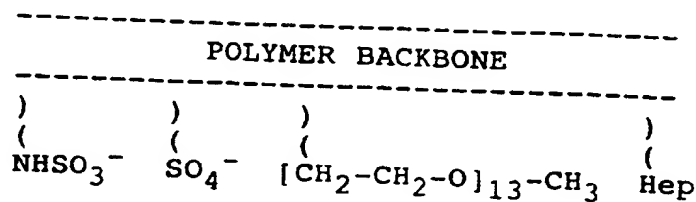


#### Example 9

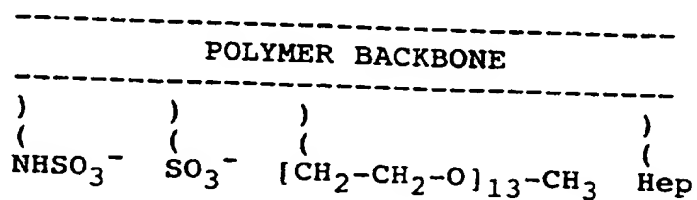
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 7.7g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 40.8g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 22.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000.

-22-

The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

Example 10

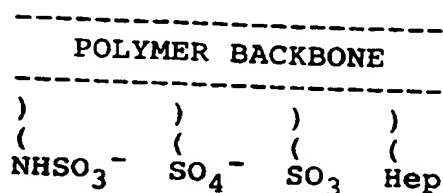
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13. 8.6g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 45.2g), vinyl sulphonic acid sodium salt (25% aqueous solution, 14.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:





Example 11

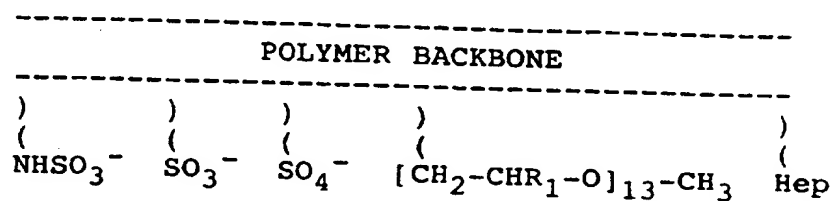
2-Sulphamatoethyl methacrylamide (25% aqueous solution, 16.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 59.6g), vinyl sulphonic acid sodium salt (25% aqueous solution, 18.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

Example 12

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.3g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 17.6g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 26.4g), vinyl sulphonic acid sodium salt (25% aqueous solution, 12.8g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to

-24-

start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



#### EXAMPLES 13 AND 14: MODIFICATION OF POLYETHYLENE IMINE (PEI)

PEI was supplied as a 50% solution in water by BASF, approximate molecular weight is 20,000.

##### Example 13

PEI (140g) was dissolved in 1 litre of isopropanol. Hexamethylene diisocyanate (2.8g) was dissolved in 50ml of acetone. The diisocyanate solution was added drop-wise to the PEI solution. The final solution was then rotary evaporated to remove the isopropanol (500ml).

##### Example 14

PEI (140g) was dissolved in 500ml of isopropanol. Hexamethylene diisocyanate (1.4g) was dissolved in 50ml of

acetone. The diisocyanate solution was added drop-wise to the PEI solution. A solution of n-butyl isocyanate (2.0g in 50ml acetone) was then added drop-wise to the solution.

#### EXAMPLES 15 AND 16: FORMATION OF SOLUTION FOR COATING

Five mole percent of acrolein is added to the monomer feed in the formation of the non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer. This allows chemical linkage to the modified polyethylene imine.

##### Example 15

The modified polyethylene imine as prepared in Example 13 is diluted to give a final composition of 0.23%. The pH of the solution is in the region of 9.5 to 10. Samples of medical devices, generally tubing, connectors and the like are coated by incubating in the solution for 10 minutes, and then washed with distilled water. Typically, the tubing may be polyvinyl chloride, polyethylene or silicone, and the connectors polycarbonate or polyvinyl chloride.

##### Example 16

The non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer is prepared as in the aforementioned Examples and is diluted with water to give a final polymer concentration of 0.08% (w/v). The pH of the solution is adjusted to 8.5 with sodium tetraborate. After the samples have been incubated in the modified polyethylene imine, as described in Example 15, the samples are incubated in the

non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer for 10 minutes. The samples are then washed and tested for haemocompatibility.

The polymer from Example 1 (non-thrombogenic polymer) and Example 8 (non-thrombogenic/anti-thrombogenic polymer) were assessed for haemocompatibility. The results showed that in both types of polymers, Example 1 (non-thrombogenic polymer) and Example 8 (non-thrombogenic/anti-thrombogenic polymer), when coated on medical devices, the blood cell and protein deposition was reduced by greater than 90% and also greatly reduced (>95%) activation of white cells, platelets and complement activation. Medical devices coated with the product of Example 8 (non-thrombogenic/anti-thrombogenic polymer) showed the additional property of reducing the thrombin-antithrombin complex concentration.

## CLAIMS

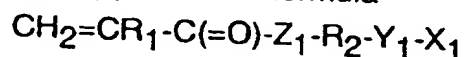
1. Polymers comprising a polymer backbone having pendant groups, obtainable by polymerizing monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

- (a) monomers having sulphate groups
- (b) monomers having sulphonate groups
- (c) monomers having sulphamate groups, and
- (d) monomers having polyoxyalkylene ether groups

2. Polymers comprising a polymer backbone having pendant groups, obtainable by polymerizing monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

- (a) monomers having sulphate groups
- (b) monomers having sulphonate groups
- (c) monomers having sulphamate groups, and
- (d) monomers having polyoxyalkylene ether groups
- (e) monomers having zwitterionic groups

3. Polymers according to Claim 1 or 2 characterized in that said monomers in Classes (a), (b) and/or (c) have the formula



where

$\text{R}_1$  is H or  $\text{CH}_3$ ;

$\text{R}_2$  is a linear or branched alkylene of 2-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure  $[\text{CH}_2-\text{CHR}_1-\text{O}]_n$  where  $\text{R}_1$  is H or  $\text{CH}_3$  and  $n$  is from 2 to 50;

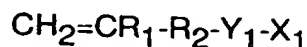
$\text{Z}_1$  is oxygen (-O-) to give an ester linkage or secondary amine (-NH-) to give an amide linkage;

$\text{Y}_1$  is (-O-) or (-NH-) or is absent; and

$\text{X}_1$  is sulphonate ( $-\text{SO}_3^-$ ).

together with an acceptable balancing cation.

4. Polymers according to Claim 1 or 2 characterized in that said monomers in Classes (a), (b) and/or (c) have the formula:



where

$\text{R}_1$  is H or  $\text{CH}_3$ ;

$\text{R}_2$  is a linear or branched alkylene of 1-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure  $[\text{CH}_2-\text{CHR}_1-\text{O}]_n$  where  $\text{R}_1$  is H or  $\text{CH}_3$  and  $n$  is from 2 to 50;

$\text{Y}_1$  is  $(-\text{O}-)$  or  $(-\text{NH}-)$  or is absent; and

$\text{X}_1$  is sulphonate  $(-\text{SO}_3^-)$ .

together with an acceptable balancing cation.

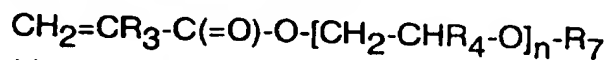
5. Polymers according to any one of Claims 1 to 4 characterized in that the monomer containing sulphate groups is selected from salts of 2-sulphatoethyl methacrylate, 2-sulphatoethyl acrylate, 3-sulphatopropyl methacrylate, 3-sulphatopropyl acrylate, 4-sulphatobutyl methacrylate, 4-sulphatobutyl acrylate, allyl sulphate, methyl allyl sulphate, 3-buten-1-sulphate, 3-buten-2-sulphate, 2-methyl-2-propane-1-sulphate, 2-methyl-3-buten-1-sulphate, 3-methyl-3-buten-1-sulphate, 2-sulphatoethyl methacrylamide, 2-sulphatoethyl acrylamide, 3-sulphatopropyl methacrylamide, 3-sulphatopropyl acrylamide, 4-sulphatobutyl methacrylamide, 4-sulphatobutyl acrylamide, sulphato polyoxyalkylene methacrylate, and sulphato polyoxyalkylene acrylate.

6. Polymers according to any one of Claims 1 to 5 characterized in that the monomer containing sulphonate groups is selected from salts of 2-sulphoethyl methacrylate, 2-sulphoethyl acrylate, 3-sulphopropyl methacrylate, 3-sulphopropyl acrylate, vinyl sulphonate, allyl sulphonate, methyl allyl sulphonate, p-styrene sulphonate, 2-acrylamide-methylpropanesulphonate, 3-sulphopropyl ethoxy methacrylate, 3-sulphopropyl ethoxy acrylate, 3-sulphopropyl polyoxyalkylene methacrylate, and 3-sulphopropyl polyoxyalkylene acrylate.

7. Polymers according to any one of Claims 1 to 6 characterized in that the monomer containing sulphamate groups is selected from salts of 2-

sulphamatoethyl methacrylate, 2-sulphamatoethyl acrylate, 3-sulphamatopropyl methacrylate, 3-sulphamatopropyl acrylate, 4-sulphamatobutyl methacrylate, 4-sulphamatobutyl acrylate, allyl sulphamate, methyl allyl sulphamate, 2-sulphamatoethyl methacrylamide, 2-sulphamatoethyl acrylamide, 3-sulphamatopropyl methacrylamide, 3-sulphamatopropyl acrylamide, 4-sulphamatobutyl methacrylamide, 4-sulphamatobutyl acrylamide, sulphamato polyoxyalkylene methacrylate and sulphamato polyoxyalkylene acrylate.

8. Polymers according to any one of Claims 1 to 6 characterized in that said monomers in Class (d) have the formula



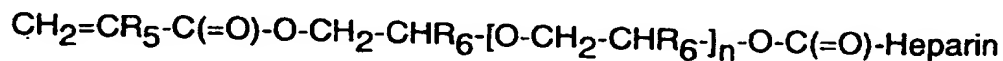
where  $\text{R}_3$  and  $\text{R}_4$ , which may be the same or different, are each H or  $\text{CH}_3$ ;  $\text{R}_7$  is H or alkyl with from 1 to 5 carbon atoms; and  $n$  is from 2 to 50.

9. Polymers according to any one of Claims 1 to 8 characterized in that said polymers comprise heparin monomer units having heparin, linked to a polymerizable moiety having a carbon-carbon double bond.

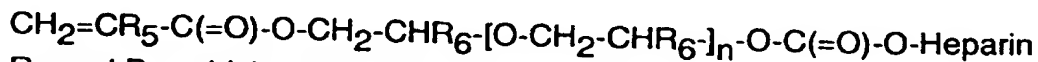
10. Polymers according to any one of Claims 1 to 8 characterized in that said polymers comprise monomer units having hirudin, warfarin or hyaluronic acid linked to a polymerizable moiety having a carbon-carbon double bond.

11. Polymers according to Claim 9 characterized in that the heparin monomer units comprise vinyl, allyl, methallyl, acrylate or methacrylate groups.

12. Polymers according to Claim 9 or 11 characterized in that the heparin monomer has the formula:



or



where  $\text{R}_5$  and  $\text{R}_6$ , which may be the same or different, are each H or  $\text{CH}_3$ ; and  $n$  is from 0 to 49.

13. Polymers according to any one of Claims 1 to 12 characterized in that said polymers contain additional monomer units derived from acrolein.

14. A medical device having a coating of a polymer according to any one of Claims 1 to 13.
15. A method of forming a coating of a polymer according to any one of Claims 1 to 14 on a medical device, characterized by forming an ungelled partial polymer by reacting a solution of an amine polymer with a crosslinking agent, activating the medical device by solution coating with said partial polymer, and depositing the polymer on the resulting activated medical device.
16. A method according to Claim 15 characterized in that the amine polymer is polyethylene imine.
17. A method according to any one of claims 15 and 16 characterized in that the crosslinking agent is an aliphatic monoisocyanate or diisocyanate.
18. A heparin monomer having the formula:  

$$\text{CH}_2=\text{CR}_5-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{CHR}_6-[\text{O}-\text{CH}_2-\text{CHR}_6]_n-\text{O}-\text{C}(=\text{O})-\text{Heparin}$$
or  

$$\text{CH}_2=\text{CR}_5-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{CHR}_6-[\text{O}-\text{CH}_2-\text{CHR}_6]_n-\text{O}-\text{C}(=\text{O})-\text{O}-\text{Heparin}$$
where  $\text{R}_5$ ,  $\text{R}_6$  and  $n$  have the meanings given in Claim 12.
19. A method of forming a heparin monomer according to Claim 16, characterized in that a hydroxyl terminated compound of the formula:  

$$\text{CH}_2=\text{CR}_5-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{CHR}_6-[\text{O}-\text{CH}_2-\text{CHR}_6]_n-\text{OH}$$
is reacted with carbonyldiimidazole to form an activated imidazolyl carbonate of the formula:  

$$\text{CH}_2=\text{CR}_1-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{CHR}_2-[\text{O}-\text{CH}_2-\text{CHR}_2]_n-\text{O}-\text{C}(=\text{O})=\text{Im}$$
wherein  $\text{R}_5$ ,  $\text{R}_6$  and  $n$  have the meanings given in Claim 18 and the activated imidazolyl carbonate is coupled with heparin at a basic pH.
20. A coating material comprising a polymer according to any one of claims 1 to 13.
21. A coating material according to Claim 20 characterized in that it is adapted for use on a surface of a medical device.



# INTERNATIONAL SEARCH REPORT

Internal J Application No  
PCT/GB 97/01173

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C08F220/28 C08F220/38 A61L33/00 C08F246/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 086 956 A (A. ARMEN) 23 April 1963 ---	
A	US 4 200 563 A (S. KOMIYA) 29 April 1980 ---	
A	WO 91 16932 A (BIOCOMPATIBLES LTD.) 14 November 1991 -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

- \* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* "&" document member of the same patent family

Date of the actual completion of the international search :

22 September 1997

Date of mailing of the international search report

~ 8. 10. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

Cauwenberg, C

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3086956 A	23-04-63	BE 573256 A DE 1469913 A FR 1239931 A GB 852399 A NL 233559 A	02-01-69 14-12-60
US 4200563 A	29-04-80	JP 1047553 C JP 53126093 A JP 55041646 B	28-05-81 02-11-78 25-10-80
WO 9116932 A	14-11-91	NONE	